REMARKS

Claims 36, 54 and 58 have been canceled, and Claims 24, 25, 33, 35, 55, 56 and 57 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention.

Independent claim 24 has been merged with cancelled claims 36 and 54. The preamble of claim 24 has been amended for particularity and clarity to replace the phrase "is associated with a germline mutation" with the phrase "is known to be associated with a germline mutation." Support for that amendment can be found in the instant application at least in the following statements at page 8, lines 3-7: "Herein are described representative assays to detect mutations in the APC gene and in MMR genes. However, ones of skill in the art can readily adapt such assays to detect analogous mutations in other genes. . . wherein such mutations are known to be associated with a disease or disease susceptibility. . . ." [Emphasis added.] In the preamble of claim 24, the phrase "that causes an about 50% decrease in the level of wild-type protein normally expressed by one of two or more subject genes" has been applied directly to the term germline mutation for purposes of particularity and clarity. Support for that amendment can be found at least on page 5, line 24 to page 6, line 20; page 9, line 22 to page 10, line 2; page 11, lines 19-21; page 19, line 27 to page 20, line 3; page 45, lines 24-29; page 49, lines 1-25; and page 50, lines 1-5.

The steps recited in Claim 24 have likewise been amended to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention. In particular, step (a), "isolating a biological sample from said organism" has been replaced with "isolating a biological sample containing normal cells from said

organism." Support for that amendment can be found in the instant application on page 12, lines 7-9, which reads "[f]urther preferred" biological samples are "normal cell samples, normal cell extracts, lysates of normal cells, and supernatants of normal cell lysates." Further support is found at least on page 30, lines 16-23.

The subsequent steps of Claim 24 have been amended to point out with particularity and clarity that it is proteins extracted from normal cells that are being measured and compared to detect whether a germline mutation is present in one of the subject genes, wherein said germline mutation is known to be associated with a disease or a disease susceptibility trait, and if present, would cause an about 50% decrease in the level of wild-type protein normally expressed. Support for those amended steps can be found on page 39, lines 9-13.

Two steps have been also added to Claim 24: new step (b), "preparing a lysate of said normal cells," and new step (c), "preparing a protein extract from said lysate of said normal cells." Support for these two additional steps can be found at least on page 12, lines 6-10; page 30, line 25 to page 31, line 2; page 38, lines 13-14; page 39, lines 9-13; page 47, lines 13-23; and page 51, lines 13-27.

The phrase "an abnormally low level" has been changed to "an about 50% decrease in the normal level" in the last two steps of Claim 24. Support for that amendment can be found in the instant application at least at page 5, lines 24-29, and at page 9, lines 22-25.

Dependent claims 25, 33, 35, and 55-57 have been amended to reflect the amendments to independent claim 24 as discussed above. Claims 36, 54, and 58 have been cancelled.

Applicant respectfully submits that no new matter has been entered by the cancellation of claims 36, 54 and 58 and the amendments to claims 24, 25, 33, 35, 55, 56 and 57.

35 USC 112, 1st Paragraph Rejection

Claims 24-28, 32-41, 43, 44 and 54-61 stand rejected under 35 USC 112, first paragraph "because the specification, while being enabling for methods where the subject genes are MLH1 and MSH2, does not reasonably provide enablement for practicing the claimed methods with any subject genes. . . ." [Office Action, pages 2.] Applicant has amended the language of Claim 24 to point out with more particularity and clarity that the claimed invention is not directed to any subject genes, but only to those subject genes known to be associated with a disease or disease susceptibility trait resulting from a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by the subject gene.

The Office Action mistakenly states on page 2, that

> the recitation 'mutations that cause an about 50% decrease in the level of wild-type protein normally expressed by a subject gene' does not confine the method to detection of disease or diseases susceptibility traits for which the teachings of the specification are enabling. Undue experimentation would be required to establish that a 50% decrease in level of wild-type protein would be associated with a disease susceptibility.

Applicant has amended the preamble of Claim 24 to clarify that the claimed invention is not directed to a method for detecting any disease or disease susceptibility trait, but only to a method for detecting those diseases or disease susceptibility traits known to be associated with a germline mutation that causes an about 50% decrease in the level

of wild-type protein normally expressed by a subject gene. Thus, the invention is not meant to be used to detect a previously unknown association between a gene and a disease or a disease susceptibility.

The Office Action at page 2 states that "[t]he amendment to claim 24 fails to limit the claimed methods to that which is enabled because the active steps remain the same." Claim 24 has been amended to point out with more particularity and clarity that the "immunologically quantitating the amount of wild-type protein" of step (d) is performed on a protein extract of a lysate of normal cells in the biological sample of step (a). Furthermore, the preamble of Claim 24 has been changed to point out with more particularity and clarity that the diseases or disease susceptibility traits detected by the invention are those "known to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by a subject gene. . . ." Further for particularity and clarity, the phrase "abnormally low" in the last two steps of Claim 24 has been changed to "about 50% decrease in the normal level" to point out with more particularity the methods of the invention.

Applicant respectfully requests that the Examiner reconsider the subject 112, first paragraph rejection in view of the amendments to the claims and the above remarks, and withdraw this rejection.

35 USC 103(a) Rejection of Claims 24-28, 31-43 and 58-61

Claims 24-28, 31-43 and 58-61 stand "rejected under 35 USC 103(a) as being unpatentable over Vogelstein et al. (WO 97/08341; published 6 March 1997) in view of Sommer (U.S. Patent 5,569,608; issued Oct. 29, 1996). . . ." [Office Action, page

3]. Applicant respectfully traverses that rejection by first relying on the arguments made in the earlier Amendments dated April 2, 2002 and Nov. 18, 2002 concerning the subject invention. The arguments and remarks made therein as well as the case law supporting those arguments and remarks are herein incorporated by reference.

Applicant respectfully traverses that rejection, arguing that he is unaware of any publication or combination of publications which suggests using the method of the present invention to detect "an about 50% decrease in the level of wild-type protein expressed by" a subject gene, wherein such an about 50% decrease signifies a germline mutation in one allele of that gene. The instant invention's nonobviousness is evident from its overcoming certain drawbacks of the prior art, including those cited by Vogelstein et al., and its filling a long-felt but unsolved need: a practical method for large-scale genetic screening for disease or disease-susceptibility. The present invention is simple, but its simplicity is evidence of its nonobviousness.

Vogelstein et al.

There is currently no simple, cost-effective, commercially-available method for genetic screening. Vogelstein et al. identified the long-felt need for the present invention, stating that "**there is a need in the art for a technique which is relatively simple to perform and which will detect a broad spectrum of mutations in genes of clinical interest**." [Vogelstein et al., page 1, second paragraph; emphasis added].

Vogelstein et al. admits to the problems of the method disclosed therein, stating: "MAMA [Mono-Allelic Mutation Analysis] has certain disadvantages as well. It

requires approximately four to six weeks to complete the analysis." [Vogelstein et al., page 6, lines 27-28.] Moreover, "[f]or the facile analysis of other hereditary diseases with MAMA, several practical criteria should be met. Rodent cell recipients should be available. Monoclonal antibodies that do not cross-react with hamster proteins simplify the analysis considerably. . . . Additionally, some mutations (e.g., tissue specific expression defect) may be difficult to detect with MAMA." [Vogelstein et al., page 7, lines 6-11.] Furthermore, Vogelstein et al. indicates that the methods disclosed therein require confirmation that the fused hybrid cells do in fact carry a human chromosome which carries the gene of interest, and that the human genes are behaving in the hybrid cell as they would in a human cell. Vogelstein et al. failed in the attempt to provide a "relatively simple to perform" screening test for germline mutations. The present invention succeeds.

The methods of Vogelstein et al. are based on somatic cell hybridization.[1] The Applicant's methods can be distinguished from Vogelstein et al. at least as follows:

1) Vogelstein et al. fuses human cells to hamster cells. The present invention lyses the cells of the subject organism.

---

[1] The methods of Vogelstein et al. require fusing human

> . . . cells to rodent cell recipients to form human-rodent cell hybrids;
>
> testing said human-rodent cell hybrids to confirm the presence of said chromosome of the human in said hybrid;
>
> testing said hybrids which contains [*sic*] said chromosome to detect a protein product of said gene, absence of said protein product or diminished amounts of said protein product indicating the presence of a mutation in the gene of interest of the human.

[Claim 1 of Vogelstein et al., page 16.]

2) Vogelstein et al. requires testing the resultant cell hybrids to confirm the presence of the human chromosome. The present invention has no such step.

3) The present invention uses an about 50% decrease in the amount of a wild-type protein expressed by a subject gene as signifying a germline mutation in one allele of that gene. Vogelstein et al. has no such suggestion.

4) The present invention uses a ratio of the wild-type protein amounts of two subject genes to address the confounding immunoassay variables. Vogelstein et al. does not suggest the use of a ratio of protein amounts.

While Vogelstein et al. claims detecting diminished amounts of protein product, the product represents hybrid protein product. How does one standardize "diminished" hybrid protein product? The only criterion for selecting the hybrid cells to be subjected to mutational analysis by Vogelstein et al. is that the cells "contain one copy of the human gene of interest from the human who is being tested. . . ." [Vogelstein et al., page 5, lines 9-10.] Every hybrid cellular environment could be different, even if each has in common one copy of the same human gene of interest. The human gene expression can be affected potentially by the particular mix of human chromosomes, homologous rodent genes or regulatory factors that are present in each hybrid. Applicant, on the other hand, analyzes normal gene expression in normal cells, and therefore can standardize the amount of wild-type protein expressed by a subject gene with the amount of wild-type protein expressed by another subject gene, and use a ratio of about 50% decrease in the normal level of a wild-type protein as the criterion for detecting a germline mutation.

Vogelstein et al. only measures hybrid proteins, expressed by only one allele, in somatic cell hybrids. The peripheral blood lymphocytes, according to the

method of Vogelstein et al., must first be fused to rodent cells and screened for the presence of the human allele in question, before being tested for protein expression. The present invention measures normally-occurring proteins, expressed by both alleles, in their normal environment.

Because Vogelstein et al. measures absent or diminished protein products of only one-half of the normal genetic complement, the "diminished" protein levels of Vogelstein et al. (i.e., from an isolated mutant allele expressing protein in a hybrid cell) will be very low, as these levels will represent reductions in protein expression levels that have already been reduced by half. In the methods of the instant application, the full genetic complement is present, expressed protein levels per cell will be much higher and should be easier to detect.

Why would it be obvious for one of skill in the art to simply lyse the cells of interest, and use an about 50% decrease in the amount of a wild-type full-length protein expressed by a subject gene to detect a germline mutation in one allele of that gene, when Vogelstein et al. emphasizes the importance of first identifying the responsible allele through the production of somatic cell hybrids? According to Vogelstein et al.,

> Analysis of the hybrids allows the observation of the product of a single human allele, without interference from the second allele's product which is present in human diploid cells. In addition, analysis of the hybrids allows identification of a haplotype which can be traced throughout the family of the individual to identify affected family members.

[Vogelstein et al., page 3, lines 24-28.]

Vogelstein et al. in fact teaches away from the development of a rapid assay for germline mutations, by stating: "It requires approximately four to six weeks to complete the analysis. Genetic diagnostic tests are generally not emergency

procedures, however, and sensitivity and specificity are far more important than immediacy in most circumstances." [Vogelstein et al., page 6, line 29-31.]

But time *is* important: for a colon cancer patient about to undergo surgery, rapid decisions must be made whether to perform a total colectomy or a partial colectomy. If the patient has a germline mutation, then the surgeon will usually perform a total colectomy, and may also alter the course of adjuvant chemotherapy. The faster the results of a germline mutation test, the sooner the patient can begin treatment.

Furthermore, time-consuming procedures are also prohibitively expensive. Unlike the methods according to Vogelstein et al., the present invention has the potential to be used also as a broad-based, automated test with widespread availability, to screen large populations for hereditary disease susceptibilities. If a symptomless individual is not tested because of expense or availibility, early detection and life-saving intervention cannot occur. The methods of the present invention fill the need for a practical clinical screening test for germline mutations, precisely because the instantly claimed methods bypass the time-consuming separation of chromosomal alleles described in Vogelstein et al.

Applicant respectfully submits that Vogelstein et al. rather than rendering the instantly claimed methods obvious, is excellent evidence of the nonobviousness of the instant claims. The applicants of Vogelstein et al., that is, Bert Vogelstein, Kenneth Kinzler and Nickolas Papadopoulos of Johns Hopkins University, are certainly ones highly skilled in the art. The Vogelstein et al. applicants state "there is a need in the art for a technique which is **relatively simple to perform** and which will detect a broad spectrum of mutations in genes of clinical interest." [Vogelstein et al., page 1, second

paragraph; emphasis added.] The Vogelstein et al. methods are certainly not "relatively simple to perform." Did the Vogelstein et al. applicants who are looking for methods "relatively simple to perform" think it was obvious to calculate a ratio between the wild-type full-length protein expressed by two subject genes? Applicant respectfully submits that Vogelstein et al. is the best evidence that the answer to that question is no.

Other attempts to develop a practical clinical test for germline mutations have resulted in even more expensive and time-consuming tests, based on nucleic acid analysis. And even such nucleic acid tests will often not identify the genetic defect. Moreover, the methods of the present invention, "by detecting the level of wild-type protein, may have greater sensitivity than the molecular genetic approaches, since they are able to detect, in addition to standard mutations, the mutations involving allelic loss, and mutations in the promoter, enhancer and splice site regions." [Instant application, page 4, lines 20-23.]

Simplicity as Evidence of Nonobviousness and Vogelstein et al.

The present invention is simple. Its very simplicity can be viewed as evidence of its nonobviousness. [See attached Enclosure 1, Section 5.04[7] and Supplemental Section 5.04[7][a](2001) from the treatise Chisum on Patents, concerning the case law.] Further enclosed in Appendix A are more details concerning the cases cited herein.

As the Court of Claims[2] noted in Palmer v. United States, 163 USPQ 250 at 254 (Ct. Cl. 1970): "[U]nder the circumstances . . . the simplicity of plaintiff's light is a hallmark of its unobviousness." [Emphasis added.] The Second Circuit in American Safety Table Co. v. Schreiber, 122 USPQ 29, 36 (2d Cir. 1959), *cert. denied,* 361 U.S. 915 (1959) stated: "[T]he very simplicity of a new idea is the truest and most reliable indication of novelty and invention."

The Court of Customs and Patent Appeals[2] stated in In re Sporck 133 USPQ 360(2) (CCPA 1962): "[T]he simplicity of new inventions is often times the very thing that is not obvious before they are made." [Emphasis added.] The Court of Claims has also stated: "Experience has shown that some of the simplest advances have been the most nonobvious." [van Veen v. United States, 151 USPQ 506 (Ct. Cl. 1967).]

Gentry Gallery, Inc. v. Berkline Corp., 41 USPQ2d 1345 (D. Mass. 1996) *aff'd in part, rev'd in part*, 45 USPQ 1498 (Fed. Cir. 1998) stated at 1349 in a case involving a one-armed sectional sofa, with a console positioned between two reclining chairs:

> **This change, which has been extraordinarily popular, certainly seems simple. Any graduate of a high school art class could design the essentials with a piece of paper and pencil in ten minutes. But no one did.**

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[2] In the Federal Circuit's first reported opinion, South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982), the Federal Circuit adopted as binding precedent "the holdings of our predecessor courts, the United States Court of Claims and the United States Court of Customs and Patent Appeals [CCPA]. . . ." [Emphasis added.]

[Emphasis added.] As in the Gentry Galley case, in the instant case there is no evidence that despite the simplicity of the claimed method that anyone else had conceived and/or reduced to practice the claimed method or any related method.

In the Gentry Gallery case, there was evidence of commercial success of the claimed one-armed sectional sofa with console and side-by-side recliners. However, in the instant case, there is no evidence of such commercial success as the application has not issued, and as the Federal Circuit and pointed out in In re Sernaker, 217 USPQ 1 at 21 (Fed. Cir. 1983) that "secondary considerations, such as commercial success, typically do not play a large part in the analysis of obviousness because the inventor usually waits until his patent issues before he swings production into full gear."

The **absence** from the market of any commercial embodiment of the claimed method could be designated as evidence of a nontraditional secondary consideration of nonobviousness. If the claimed invention in all its simplicity were obvious, wouldn't a commercial assay embodying the claimed method be on the market today? As the Federal Circuit stated in Stratoflex, Inc. v. Aeroquip Corp., 218 USPQ 871 at 879 (Fed. Cir 1983):

> **[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record**. It may often establish that an invention appearing to be obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.

[Emphasis added.] The absence from the market of products within the scope of the Applicant's inventive concept is considered nontraditional, as secondary considerations of nonobviousness based upon commercial success are usually presented in

infringement litigation.[3] In the instant situation, the absence of a commercial embodiment on the market, in view of the simplicity of the claimed invention and the stated need for such assays as indicated by Vogelstein et al., reflects strongly upon its nonobviousness.

Applicant respectfully submits that the present invention fills a long-felt need, while overcoming the expense, complications and lengthy procedures of the prior art, including Vogelstein et al. The present invention is easily understood in hindsight, but if it were obvious at the time it was made (the time that counts in considering obviousness), why was it not used before in view of the need for "relatively simple to perform" methods to detect germline mutations in genes of clinical interest?

Sommer et al.

The Office Action on page 3, section 5 states: "In view of the teachings of Sommer, that calculation of a ratio in the quantification of immunological measurements is known in the art, and in view of the fact that the amendment is to the preamble of the

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[3] As the Federal Circuit pointed out in In re Sernaker, 217 USPQ 1 at 21 (Fed. Cir. 1983):

> In an appeal of a rejection of a patent application, secondary considerations, such as commercial success, typically do not play a large part in the analysis of obviousness because the inventor usually waits until his patent issues before he swings production into full gear. Thus, a detailed analysis of secondary consideration is more common in cases like John Deere, which involved infringement. If however, a patent application properly presents evidence relating to secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.

[Emphasis added.]

claims and not to the active steps, the rejection is maintained." Applicants respectfully traverse that rejection.

The Sommer reference describes a method of quantifying the concentrations of an analyte separated by immunochromatography and labeled by a tracer that binds it during the separation, by comparing its tracer signal with a standard curve prepared from known concentrations of the same analyte with the tracer. While Sommer teaches that the calculation of a ratio in the quantification of immunological measurements is known in the art, it does not contain disclosures concerning calculating a ratio or ratios of the amounts of wild-type protein expressed by subject genes for use in detecting germline mutations, nor does it indicate how to eliminate the additional lengthy experimentation of Vogelstein et al. to detect the presence of germline mutations. Applicant respectfully submits that nothing in Sommer adds to the disclosure of Vogelstein et al. to render the present invention obvious.

Applicant respectfully concludes neither Vogelstein et al. alone or in view of Sommer renders the instantly claimed invention obvious, but instead as explained above is evidence of the nonobviousness of the instant invention. The very simplicity of the claimed methods is "a hallmark of its unobviousness." [Palmer v. United States, supra at page 254.] Applicant respectfully requests that the Examiner reconsider the instant rejection in view of the above remarks and case law, and withdraw the 103(a) rejection.

35 USC 103(a) Rejection of Claims 24, 44 and 61

Claims 24, 44 and 61 stand rejected under 35 USC 103(a) as being unpatentable over Vogelstein et al. (WO 97/08341; published 6 March 1997) in view of Sommer (U.S. Patent 5,569,608; issued Oct. 29, 1996); and further in view of Kinzler et al (U.S. Patent 6,048,701; issued April 11, 2000; effective filing date June 7, 1995), "for the reasons of record. . . ." [Office Action, page 3, section 6.] The Office Action of July 16, 2002 states at page 6: "Claim 44 is drawn to methods where the protein detection is automated. Vogelstein and Sommer teach as described above, but fail to teach automated immunological methods. However, automated immunological methods are well known in the art as evidenced by the teachings of Kinzler." Applicant respectfully traverses this rejection relying upon again the arguments made in the responses dated April 2 and Nov. 18, 2002, and arguments made above in response to the obviousness rejection over Vogelstein et al. in view of Sommer.

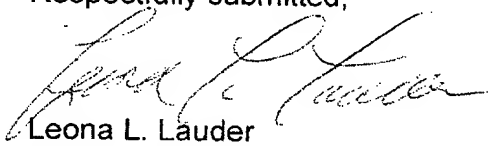
Kinzler et al. contains no disclosures concerning calculating a ratio or ratios of the amounts of wild-type protein expressed by subject genes for use in detecting germline mutations. Since nothing in Kinzler et al. adds to the disclosure of Vogelstein et al., alone or in combination with Sommer, to render claim 24 obvious, claims 44 and 61 are similarly nonobvious in view of In re Fine, 5 USPQ2d 1596 at 1600 (Fed. Cir. 1988): "Dependent claims are nonobvious under Section 103 if the independent claims from which they depend are nonobvious."

Applicant respectfully concludes that neither Vogelstein et al., Sommer nor Kinzler et al., alone or in any combination, render the instantly claimed invention obvious. Applicant respectfully requests that the Examiner review this rejection in view of the above amendments and remarks, and withdraw this rejection.

CONCLUSION

Applicant respectfully concludes that the claims as amended are in condition for allowance, and earnestly requests that the claims be promptly allowed. If for any reason Examiner feels that a telephone conference be helpful, the Examiner is invited to telephone the undersigned Attorney for Applicant at (415) 981-2034.

Respectfully submitted,



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[a]—"Simple" Inventions. An invention that seems "simple" was not necessarily obvious before it was made. Indeed, an invention's simplicity may support a conclusion of unobviousness.[2.1]

In *In re Sporck* (1962),[2.2] the Court of Customs and Patent Appeals noted that "the simplicity of new inventions is often times the very thing that is not obvious before they are made."[2.3]

Compare *In re* Mixon, 470 F.2d 1374, 1377, 176 USPQ 296 (CCPA 1973); Omark Indus., Inc. v. Colonial Tool Co., 672 F.2d 362, 365, 217 USPQ 13, 15 (3d Cir. 1982) ("We agree with plaintiff that simplicity in and of itself is not fatal to patentability. However, when a simple device is clearly anticipated by equally simple prior art, nothing is gained by an extended discussion of precedents which wrestle with far more complex issues."); Eisele v. St. Amour, 423 F.2d 135, 137, 165 USPQ 161 (6th Cir. 1970); Ludwig Drum Co. v. Solar Musical Instru. Co., 376 F.2d 827, 830, 153 USPQ 579 (6th Cir. 1967); United States Tel. Co. v. American Telecommunications Corp., 204 USPQ 951, 955 (D. Conn. 1979) ("Simplicity of construction is not automatically entitled to a patent. The simplified method must still be one that is not obvious to those with ordinary skill in the art. . . .").

2.1 E.g. Roberts v. Sears, Roebuck & Co., 723 F.2d 1324, 221 USPQ 504 (7th Cir. 1983), *further proceedings*, 4 USPQ2d 1527 (N.D. Ill. 1987) (not proper to deny patentability solely because of simplicity of device); Globe Linings, Inc. v. City of Corvallis, 555 F.2d 727, 730, 194 USPQ 415, 418 (9th Cir.), *cert. denied*, 434 U.S. 985 (1977) ("An inventor will not be denied a patent simply because his invention embodies a solution which seems simple and obvious with the benefit of hindsight."); Henkel Corp. v. Coral Inc., 754 F. Supp. 1280, 1315, 21 USPQ2d 1081, 1106 (N.D. Ill. 1990), *aff'd*, 945 F.2d 416 (Fed. Cir. 1991)(unpublished) ("The apparent simplicity of a claimed invention does not render it more easily invalidated. . . . [T]o equate simplicity with obviousness is an erroneous concept."); Dolly Inc. v. Spalding & Evenflo Companies Inc., 18 USPQ2d 1737, 1751 (S.D. Ohio 1991) ("The relative simplicity of a device does not render the claimed invention obvious."); Creative Pioneer Products Corp. v. K Mart Corp., 5 USPQ2d 1841, 1844 (S.D. Tex. 1986)("A simple invention is not necessarily an obvious one."); State Industries, Inc. v. Mor-Flo Industries, Inc., 639 F. Supp. 937, 945, 231 USPQ 242, 247 (E.D. Tenn. 1986), *aff'd*, 818 F.2d 875 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 845 (1987) ("The invention here in dispute is simple and there is an inclination to find such simple things to be obvious. However, if the invention were so obvious why hadn't anyone come up with it . . .?").

2.2 301 F.2d 686, 133 USPQ 360 (CCPA 1962).

2.3 301 F.2d at 689, 133 USPQ at 363.

See also *In re* Osplack, 195 F.2d 921, 924, 93 USPQ 306, 308 (CCPA 1952) ("simplicity may even be some evidence of invention").

Enclosure 1

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In *van Veen v. United States* (1967),[2.4] the Court of Claims noted that "[e]xperience has shown that some of the simplest advances have been the most nonobvious."[2.5]

In *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.* (1988),[2.6] the Federal Circuit noted that "the patent statute [does not] require that an invention be complex in order to be nonobvious."[2.7]

[b]—Slight or Minor Changes. Judge Learned Hand emphasized that "[n]othing is easier in patent litigation than to confuse a trifling physical change with the ingenuity demanded for its discovery."[2.8]

In *Speed Shore Corp. v. Denda* (1979),[2.9] the Ninth Circuit noted that "even a minor change may produce a patentable invention, where the result could not have been predicted beforehand by one skilled in the art."[2.10]

[2.4] 386 F.2d 462, 465, 151 USPQ 506 (Ct. Cl. 1967).

[2.5] 386 F.2d at 465, 151 USPQ at 508.

See also Palmer v. United States, 423 F.2d 316, 321-22, 163 USPQ 250, 254 (Ct. Cl. 1970) ("under the circumstances . . . the simplicity of plaintiff's light is a hallmark of its unobviousness.").

[2.6] 851 F.2d 1387, 1390-91, 7 USPQ2d 1222, 1225 (Fed. Cir. 1988).

[2.7] 851 F.2d at 1390-91, 7 USPQ2d at 1225.

See also *In re* Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992) ("Simplicity is not inimical to patentability."); Continental Can Company USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1751 (Fed. Cir. 1991) ("the criterion of § 103 is not whether the differences from the prior art are 'simple enhancements', but whether it would have been obvious to make the claimed structure.").

[2.8] Refractolite Corp. v. Prismo Holding Corp., 117 F.2d 806, 807, 48 USPQ 497 (2d Cir. 1941).

See also H.C. White Co. v. Morton E. Converse & Son Co., 20 F.2d 311, 313 (2d Cir. 1927) ("the fact that the changes were so slight is quite irrelevant, so long as they were essential to the purpose, as they were. While the statute grants monopolies only for new structures, and not for new uses, invention is not to be gauged by the necessary physical changes, so long as there are some, but by the directing conception which alone can beget them.").

[2.9] 605 F.2d 469, 203 USPQ 807 (9th Cir. 1979).

[2.10] 605 F.2d at 472, 203 USPQ at 810.

See also Omark Indus., Inc. v. Textron, Inc., 688 F.2d 1242, 216 USPQ 749 (9th Cir. 1982); Continental Oil Co. v. Cole, 634 F.2d 188, 193, 209 USPQ 361, 365 (5th Cir. 1981), *reh'g denied*, 638 F.2d 1234 (5th Cir.), *cert.*

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additional antigens. In this case, the applicants point to the low *intensity* of the immune response in the claimed compound as an unexpected result. Specificity is not always commensurate with the intensity of a response." *Id.*

The Barrett reference "states that 'terminal substitutes [like Phe–Pro–Leu] often exert a controlling influence on the *specificity* of antibodies.' (Emphasis added.) Barrett does not establish the relative immunogenicity of the claimed amino acid sequences." *Id.*

The Bick reference "is not controlling. Bick notes that applicants' compounds produce a low immune response in dairy cattle. Bick however compared applicants' product to 'conventional foreign substances,' without noting whether 'conventional foreign substances' were self–proteins with small peptides attached (as in the claimed compounds) or foreign proteins. In fact, Bick even suggests that the dairy cattle should not mount a strong response because they 'should recognize the recombinant product as similar to "self."' " *Id.*

114.11 "The specification demonstrates the biological activity of the product by a study involving its use in rats. The Board dismissed this, stating 'the specification fails to explain the significance, or the applicability, of the data.' Moreover, applicants have made no attempt to show that BGH or HGH would be expected to be biologically inactive when fused to similar, recognized enterokinase cleavage sites." 104 F.3d at 1344, 41 USPQ2d at 1455–56.

[7]—Source of the Problem—Simplicity of the Solution

[a]—"Simple" Inventions

N. 2.7 See also Ruiz v. A.B. Chance Co., 234 F.3d 654, 664, 57 USPQ2d 1161, 1166 (Fed. Cir. 2000) ("The necessity of *Graham* findings is especially important where the invention is less technologically complex . . . ."); *In re* Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313 (Fed. Cir. 2000) ("idea" in a patent's claims was a technologically simple concept: "With this simple concept in mind, the Patent and Trademark Office found prior art statements that in the abstract appeared to suggest the claimed limitation. But, there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the inventor's] invention to make the combination in the manner claimed."); Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1478, 45 USPQ2d 1498, 1502 (Fed. Cir. 1998) (an accused infringer did not prove that the patented invention, a sectional sofa with two reclining seats facing in the same direction, was obvious at the time the invention was made, even if it involved only an "apparently facile combination" of two prior art devices: "even if the claimed invention did only involve the physical insertion of Talley's free–standing recliner into Kanowsky's sectional sofa, such simplicity alone is not determinative of obviousness. *See In re Oetiker*, . . . (Fed. Cir. 1992) ('Simplicity is not inimical to patentability.')."); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) (the district court erred in holding the patent in suit, which claimed a salt impregnated plastisol fishing lure, invalid for obviousness: "Commercial success and copying are tributes to ingenuity, not evidence of legal obviousness. This rule is no less worthy when the new product narrowly fits into a field already well explored—like the fishing lure art—than when a transcendent scientific breakthrough is launched. The patent law is designed to serve the small inventor as well as the giant research organization."); Para-Ordnance Manufacturing, Inc. v. SGS Importers International, Inc., 73 F.3d 1085 1092, 37 USPQ2d 1237, 1243 (Fed. Cir. 1995) (Archer, dissenting: "A simple invention may be patentable, even if the invention comprises the combination of features known in the art, provided the combination itself is not obvious."); Amazon.com Inc. v. Barnesandnoble.com Inc., 73 F. Supp.2d 1228, 1242, 53 USPQ2d 1115, 1126 (W.D. Wash. 1999), *vacated & remanded*, 239 F.3d

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1343, 57 USPQ2d 1747 (Fed. Cir. 2001) (an accused infringer's "reliance on the simplicity of the invention is unavailing."); Winner International Royalty Corp. v. Wang, 11 F. Supp. 2d 18, 24, 48 USPQ2d 1139, 1144 (D. D.C. 1998) ("simplicity alone cannot be determinative of obviousness."); Gentry Gallery Inc. v. Berkline Corp., 939 F. Supp. 98, 102, 41 USPQ2d 1345, 1349 (D. Mass. 1996), *aff'd in part, rev'd in part*, 134 F.3d 1473, 45 USPQ 1498 (Fed. Cir. 1998) ("This change, which has been extraordinarily popular, certainly seems simple. Any graduate of a high school art class could design the essentials with a piece of paper and pencil in ten minutes. But no one did."); Weatherchem Corp. v. J.L. Clark, Inc., 937 F. Supp. 1262, 1278 (N.D. Ohio 1996) ("The criteria of § 103 is not whether the differences from the prior art are 'simple enhancements,' but whether it was obvious to make the total structural combination. Simplicity is not inimical to patentability. . . . Complexity is not a requirement for non-obviousness.").

Compare Liberty Leather Products Co., Inc. v. VT International Ltd., 894 F. Supp. 136, 137, 37 USPQ2d 1342, 1343 (S.D.N.Y. 1995) ("This case for patent infringement centers on the sort of dispute over a mere improvement in gadgetry from which the United States Supreme Court sought to liberate the Federal District Courts with its opinion in *Graham v. John Deere Co.* . . . .").

[b]—Slight or Minor Changes

N. 2.12 See also *In re* Chu, 66 F.3d 292, 298, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995) ("In a proper obviousness determination, '[w]hether the changes from the prior art are "minor". . . . the changes must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the patentee's . . . device.' . . . This includes what could be characterized as simple changes, as in *In re Gordon* . . . (Although a prior art device could have been turned upside down, that did not make the modification obvious unless the prior art fairly suggested the desirability of turning the device upside down.)."); Database Excelleration Systems Inc. v. Imperial Technology Inc., 50 USPQ2d 1527, 1532 (N.D. Calif. 1999) ("even assuming a minimal difference between [the prior art] older products and the claimed invention, the enhanced performance apparently achieved by the . . . more recent . . . products suggests that the claimed invention may not have been obvious.").

[c]—Discovering a Problem's Source

[ii]—Lower Court Decisions

N. 7 See also *In re* Zurko, 111 F.3d 887, 890, 42 USPQ2d 1476, 1479 (Fed. Cir. 1997), *reh'g in banc granted*, 116 F.3d 874 (Fed. Cir. 1997), *rev'd*, 142 F.3d 1447, 46 USPQ2d 1691 (Fed. Cir. 1998), *rev'd sub nom.* Dickinson v. Zurko, 119 S. Ct. 1816, 50 USPQ2d 1930 (1999), discussed at § 11.06[3][b][v] *supra* ("[T]o say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art. *See In re Sponnable* . . . (CCPA 1969) ('[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.').").

[iii]—New Problems—Old Solutions

N. 11 Cf. Gambro Lundia AB v. Baxter Healthcare Corp., 896 F. Supp. 1522 (D. Colo. 1995), *rev'd*, 110 F.3d 1573, 42 USPQ2d 1378 (Fed. Cir. 1997) (invention obvious because, inter alia, "once the problem . . . was recognized, development of the solution . . . was 'trivial' ").

APPENDIX A

1. Palmer v. United States, 163 USPQ 250 (Ct. Cl. 1970) concerned a patent for a battery-operated electric lamp secured to a fillable ballast bag, for use as a portable lamp for landing strips. The plaintiff patent owner sued the U.S. government for its unauthorized use of a device similar to the plaintiff's patented invention. The defendant government argued that the patent was invalid for obviousness. The court upheld the validity of the lamp patent, and found that plaintiff should be awarded compensation, as the lamp used by the government infringed the patented lamp. In the opinion, the court noted at about page 254:

> [T]he prior devices show that despite no dearth of activity in the art of portable emergency lights...no one came up with Palmer's simple but highly practical idea until 1953, even though the problem of adequate aircraft emergency lights is as old as flying itself. This is persuasive evidence of unobviousness. Also pertinent is the fact that for the most part, the prior art devices are relatively complicated and expensive to make and repair, and are not adaptable for use over a wide range of operating conditions. Under the circumstances, therefore, the simplicity of plaintiff's light is a hallmark of its unobviousness.

2. The Second Circuit in American Safety Table Co. v. Schrieber, 122 USPQ 29 (2d Cir. 1959), *cert. denied*, 361 U.S. 915 (1959) concerned a collar shaping and pressing machine. Plaintiff and defendants cross-appealed the U.S. District Court (New York) determinations of patent validity and infringement with reference to plaintiff's two patents and a charge of unfair competition. The Second Circuit upheld the validity of the first patent, stating at about page 35:

> The novelty and essence of Voigt's invention was in conceiving that the application of parallel pressure to a substantial portion of the collar would produce the most effectively pressed and shaped collar. It is only after the event that the very simplicity of this ingenious contrivance makes it seem simple and obvious. The fact is that several other inventors who conceived an abundance of original thought on the subject of how to press and shape a smooth collar did not think of it. And it is only by an elaborate and detailed study of the alternate ideas suggested by others that an observer can appreciate the merit of Voigt's conception. . . .

And summarizing the court's finding, upholding the validity of the first patent at about page 36,

> In the last analysis the burden of Schreiber & Goldberg's attack on the first patent for lack of invention comes down to its simplicity. But experience in practically every field of human endeavor has demonstrated that the very simplicity of a new idea is the truest and most reliable indication of novelty and invention, when others have devoted extensive effort and exhausted their resourcefulness in a futile search for the solution of the same vexing problem.

3. In re Sporck, 133 USPQ 360 (CCPA 1962) concerned a method of forming hollow cones from metal. Appellant sought review of a decision from the U.S. Patent Office Board of Appeals, which had affirmed the rejection of the patent claims for a method as being obvious under 35 USC 103. The U.S. Court of Customs and Patent Appeals reversed the previous decision by the board, stating at about page 365:

> The fact that the invention seems simple after it is made is not determinative of the question of obviousness. If this were the rule, many of the most beneficial patents would be stricken down. If those skilled in the mechanical arts are working in a given field and have failed to discover a certain new and useful improvement, the one who first makes the discovery frequently has done more than make an obvious

> improvement which would have suggested itself to a mechanic skilled in the art, and such an invention is entitled to the grant of a patent thereon.

4. In van Veen v. United States, 151 USPQ 506 (Ct. Cl. 1967), a patentee successfully sued the U.S. government for its unauthorized use of an apparently simple patented device, a survival-type sleeping bag with insulated seams for additional warmth. The defendant government argued that the patent was invalid for obviousness. In its decision upholding the validity of the patent, the Court of Claims stated at about page 509:

> It is incorrect to hold that an invention was obvious when made, simply because the invention is simple in nature and is easily understood when described in a patent specification. Experience has shown that some of the simplest advances have been the most nonobvious.

5. Gentry Gallery, Inc. v. Berkline Corp., 41 USPQ2d 1345 (D. Mass 1996), *aff'd in part, rev'd in part*, 45 USPQ 1498 (Fed. Cir. 1998) concerned a patent covering a one-armed sectional sofa, with a console positioned between two reclining chairs. The plaintiff patent owner (Gentry Gallery) sued Berkline for infringing the patent, and the defendant Berkline defended itself by arguing among other arguments that the patent was invalid for obviousness. The District Court of Massachusetts stated at about page 1348:

> To fairly weigh a claim of obviousness, the court must, to some extent, place itself in a time machine; it must look at the invention with the eyes of an ordinary artisan living at the time the invention was made. This viewpoint is essential because many inventions, perhaps most, are obvious in hindsight and seem simple. As the Court of Appeals has said, "Simplicity is not inimical to patentability." In re Oetiker, 977 F.2d 1443, 147 (Fed. Cir. 1992).

The District Court then went back in time to when the subject invention

> was born in response to a reality as homely as the human heart: two people watching television like to sit next to each other. This predilection became complicated as more and more Americans discovered that they also liked to watch television from a big comfortable chair with a mechanism that allowed it to tilt back – a recliner. Companionship and comfort could be achieved by the purchase of two recliners placed side-by-side and facing the TV, but this arrangement, in many people's eyes, made the living room look ugly and encumbered.
>
> . . . .
>
> . . . Prior to the . . . [subject] patent it was not uncommon for a single recliner to be incorporated into a sectional set-up, or even two recliners, so long as the two recliners were at the opposite ends of the "L" – that is, on different sides of the wedge, at right angles to each other. Before the Gentry invention, however, no one had every manufactured a one-armed sectional sofa containing two recliners to be arranged on the same side of the wedge – that is, in a manner that permitted two people to sit next to each other in the recliners and watch television facing the same direction. This fact is undisputed.
>
> **This change, which has been extraordinarily popular, certainly seems simple. Any graduate of a high school art class could design the essentials with a piece of paper and pencil in ten minutes. But no one did.**

[*Id.* at 1349; emphasis added.]

6. Stratoflex, Inc. v. Aeroquip Corporation, 218 USPQ 871 (Fed. Cir. 1983) concerned a patent for bi-layered composite tubing. Appellee began manufacturing a similar tube, and brought an action seeking a declaratory judgment that the appellant's patent was invalid. Appellant sought review of the decision by the U.S. District Court for the Eastern District of Michigan, that the

appellant's patent was invalid for lack of nonobviousness. In reversing the previous decision and upholding the validity of the patent, the Federal Circuit noted at about page 879:

> It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness. Indeed, evidence of "secondary considerations" may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.